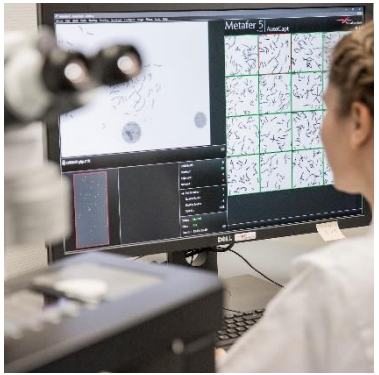
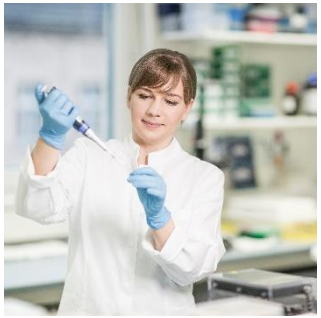
IMPLEMENTATION OF OPTICAL GENOME MAPPING IN A CYTOGENETIC CLINICAL LABORATORY



Technical Workshop

Bionano Genomics, 18.03.2022



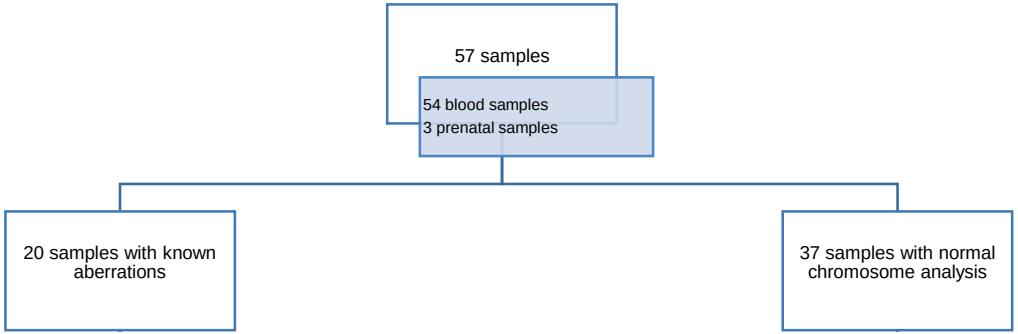
methods

method	limitation
Chromosome analysis	5-10 Mb resolution
Fluorescence *in situ* hybridisation	Targeted analysis
microarray	Detection of balanced SVs not possible

OGM since september

www.bionanogenomic.com

Results

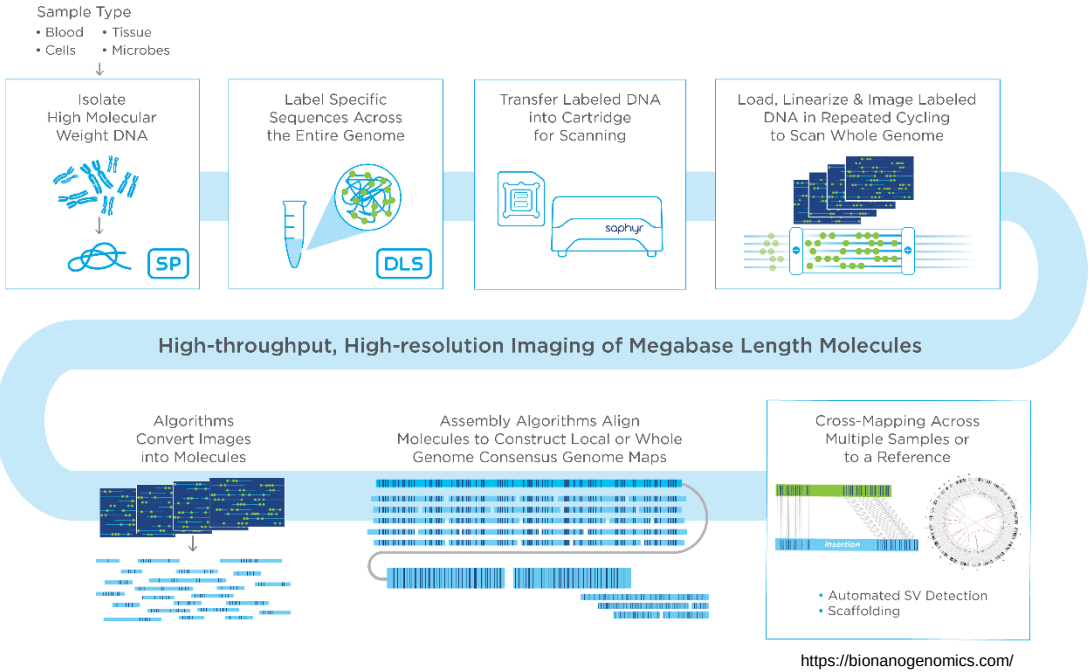

57 samples
54 blood samples
3 prenatal samples
20 samples with known aberrations
37 samples with normal chromosome analysis

Reasons for CA/FISH/microarray

- postnatal: - developmental delay, mental disability, congenital malformations
  - fertility disorders
  - known familial chromosome abnormalities

- prenatal: - abnormal ultrasound

Optical genomic mapping - *Workflow*



https://bionanogenomics.com/

Bionano Prep SP Blood and Cell Culture DNA Isolation Kit

Bionano Prep DLS Labeling Kit

Filtersettings

Samples with known aberrations

Exclude common SVs
(> 1% in BNC)
→ If normal: > 5% in BNC

“SV masking” (genomic regions that are prone to false positive calls)

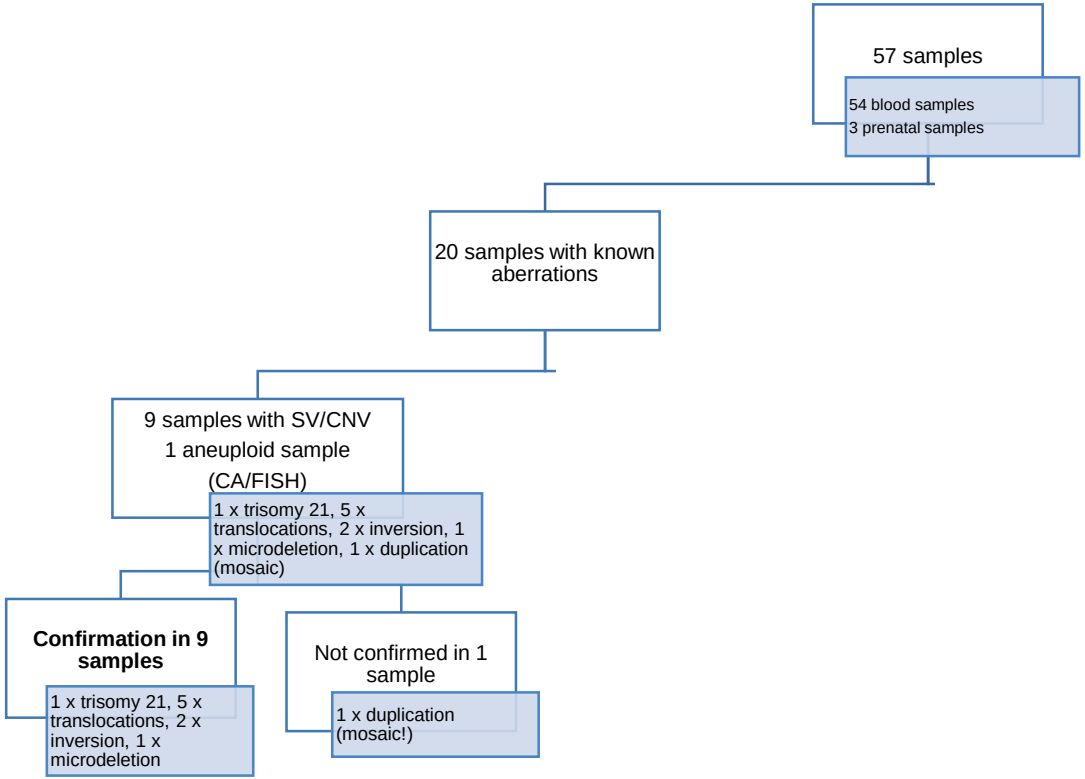
Samples without known aberations

Exclude common SVs
(> 1% in BNC)
→ If normal: > 5% in BNC

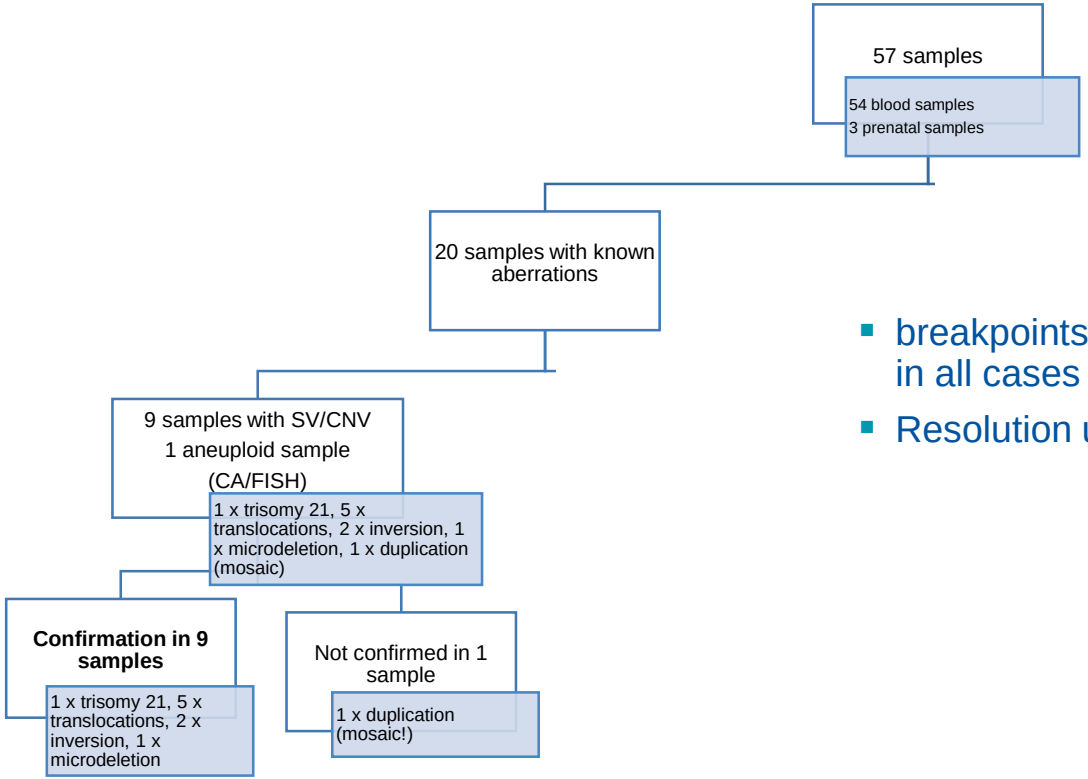
“SV masking” (genomic regions that are prone to false positive calls)

Genlists
(Human Phenotype Ontology (HPO)- terms, genes from literature)

Results

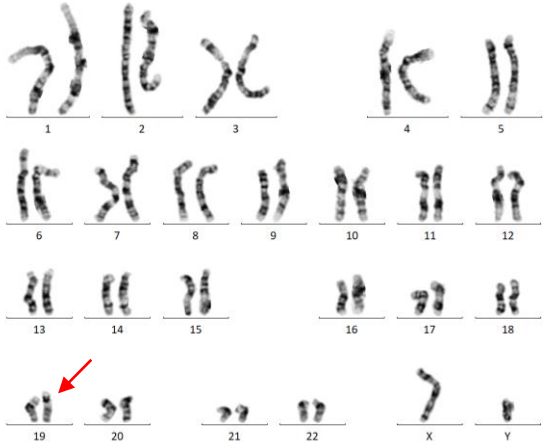

57 samples
54 blood samples
3 prenatal samples
20 samples with known aberrations
9 samples with SV/CNV
1 aneuploid sample
(CA/FISH)
1 x trisomy 21, 5 x translocations, 2 x inversion, 1 x microdeletion, 1 x duplication (mosaic)
Confirmation in 9 samples
1 x trisomy 21, 5 x translocations, 2 x inversion, 1 x microdeletion
Not confirmed in 1 sample
1 x duplication (mosaic!)

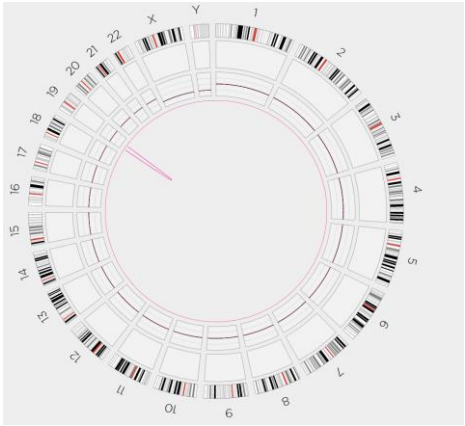
Results



- breakpoints were matching the karyotyping results in all cases
- Resolution up to gene level

Case 1: 46,XY,inv(19)(p13.3q13.1)





inv(19)(p13.2q12)

BP1: 19p: 7509755-7522480 (12,7 kb)

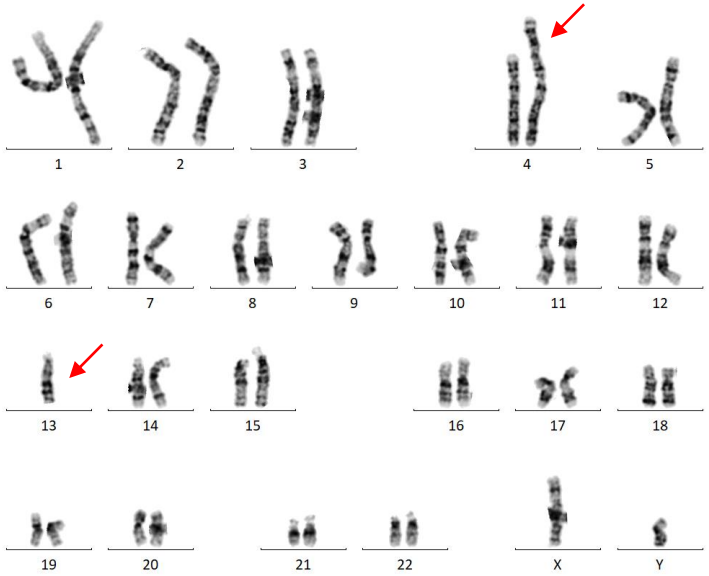
- *ARHGEF18* (OMIM #671433: RETINITIS PIGMENTOSA 78; RP78, **AR**)

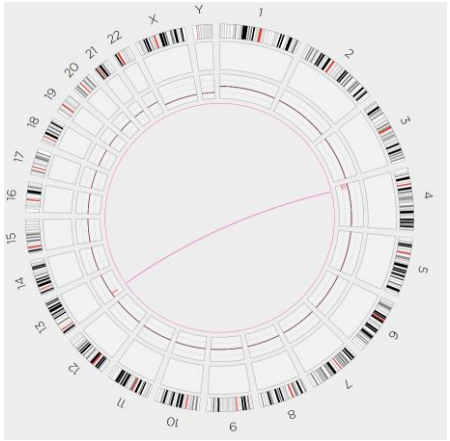
BP2: 19q: 29680116-29668205 (11,9 kb):

- Kein Gen im BP-Bereich

Case 2: 45,XY,der(4)t(4;13)(p15.2;q12),-13

- prenatal: abnormal US

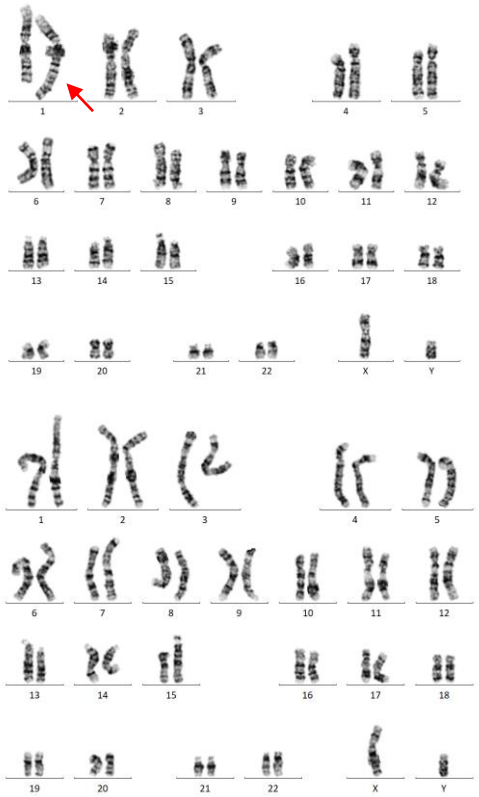


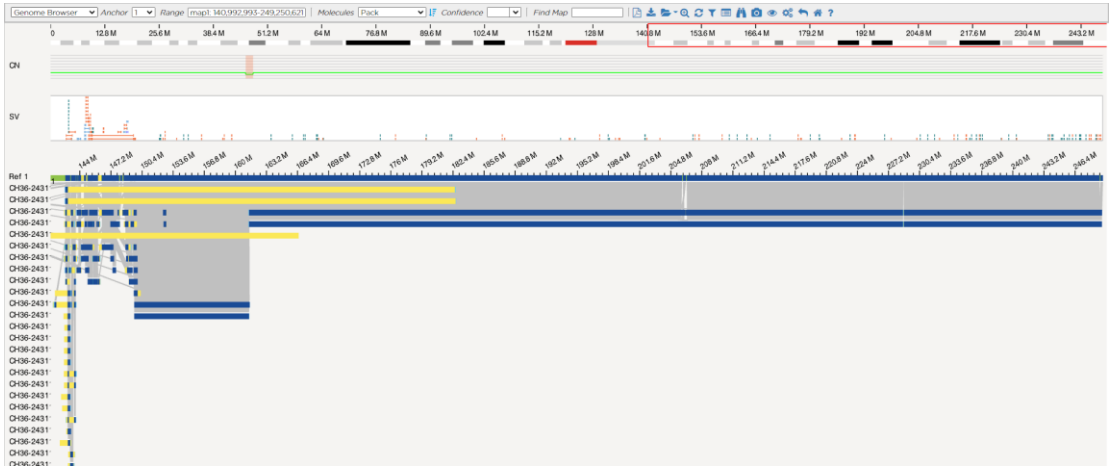


→ **4p15.31**

→ **13q12.11**

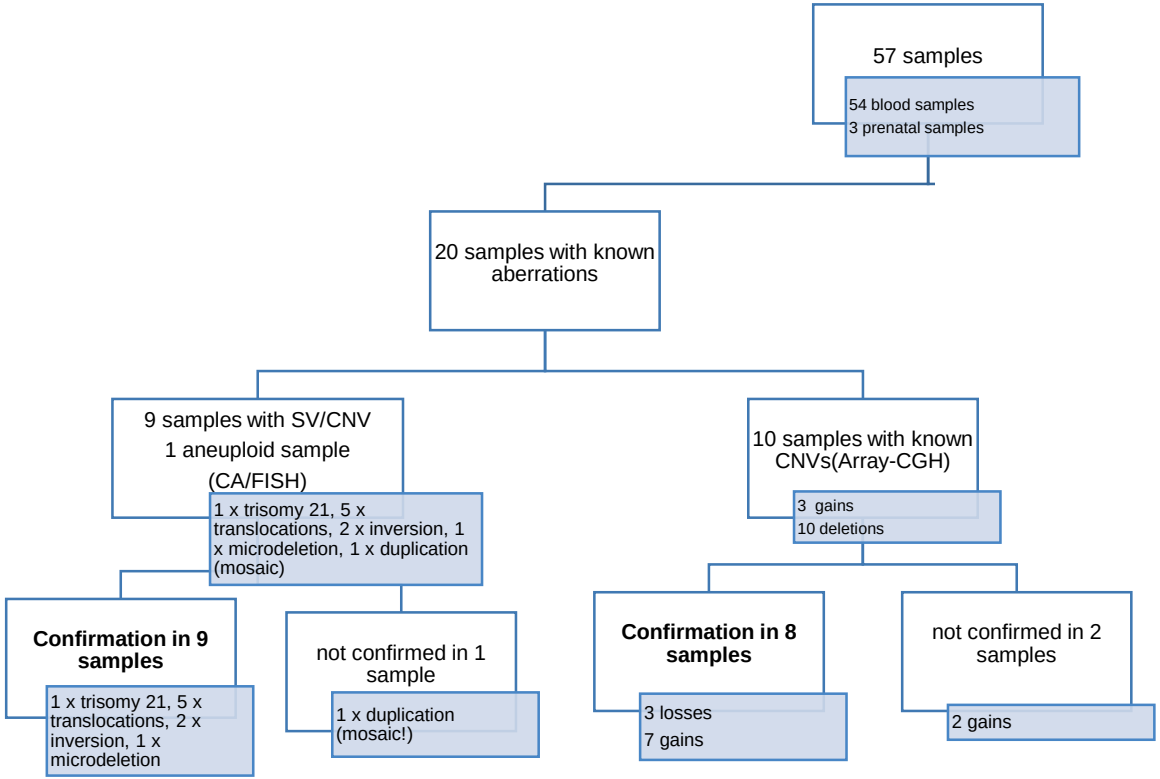
Case 3: mos 46,XY,dup(1)(pter->q44::q44->q21)[15]/46,XY[15].ish dup(1)(wcp1+)





Difference in mosaic distribution between cultures?

Results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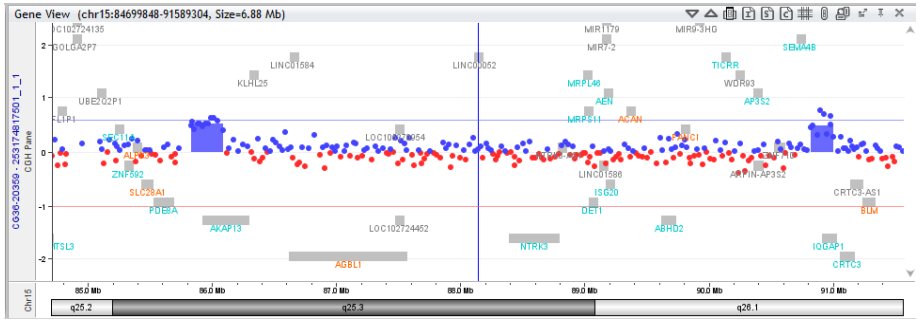
3 prenatal samples
20 samples with known aberrations
9 samples with SV/CNV
1 aneuploid sample
(CA/FISH)
1 x trisomy 21, 5 x translocations, 2 x inversion, 1 x microdeletion, 1 x duplication (mosaic)
10 samples with known CNVs(Array-CGH)
3 gains
10 deletions
Confirmation in 9 samples
1 x trisomy 21, 5 x translocations, 2 x inversion, 1 x microdeletion
not confirmed in 1 sample
1 x duplication (mosaic!)
Confirmation in 8 samples
3 losses
7 gains
not confirmed in 2 samples
2 gains

Case 4: Gains on chromosome 15

Array-CGH



→ ca. 250 kb
→ ca. 180 kb

→ complex structural variant?

Case 4: gains on chromosome 15

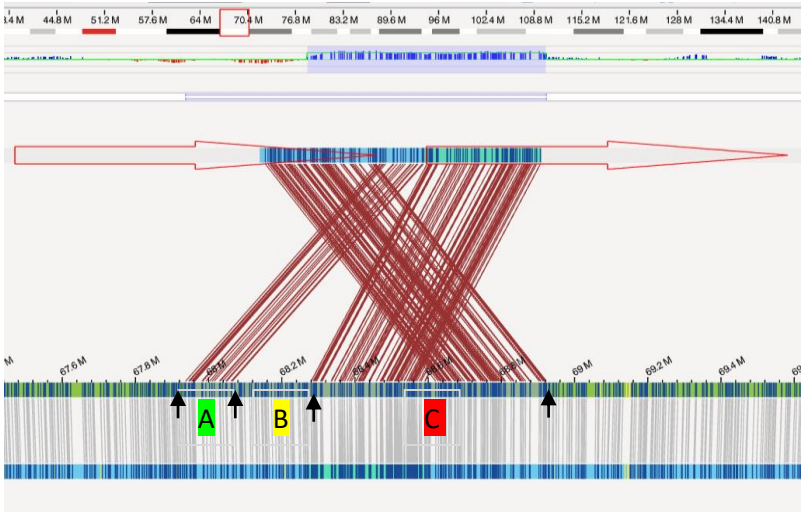
BP1: 85775165-85771461 → kein proteinkodierendes Gen
BP2: 86111313-86100128 → *AKAP13*

BP3: 90995567-91006432→ *IQGAP1*
BP4: 90715181-90716659 → kein proteinkodierendes Gen

Case 5: gains on chromosome 4

complex structural variant?

Case 5: gains on chromosome 4



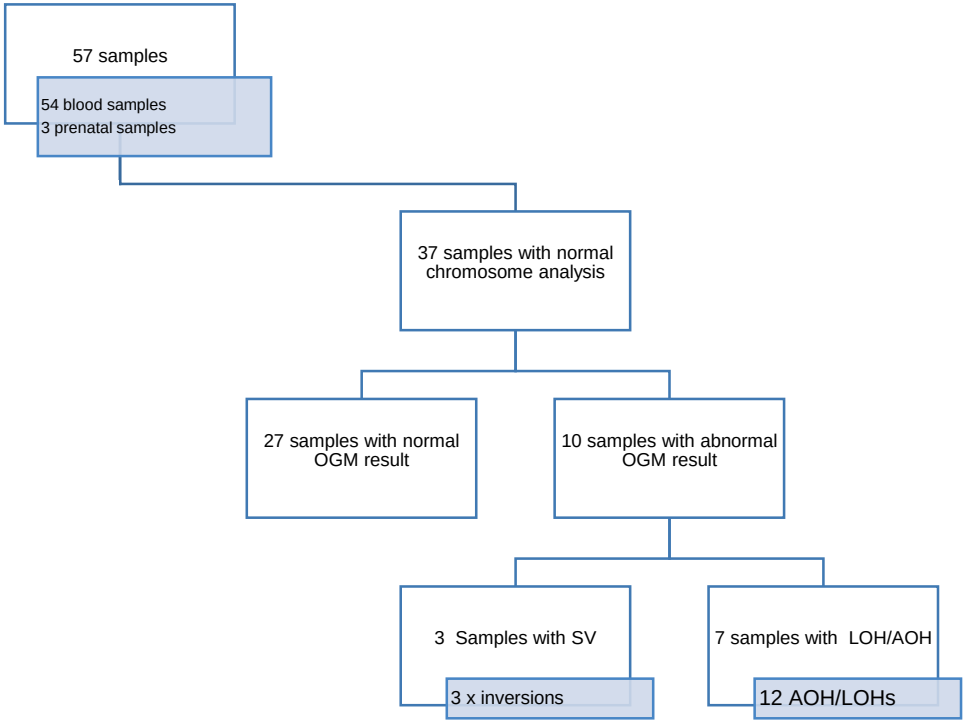
BP1: 67,934,802-67,937,075 (2,3 kb): intergenic

BP2: 68,064,795-68,071,968 (7,2 kb): intergenic

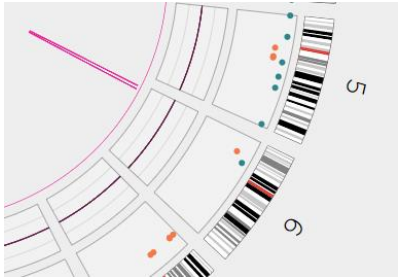
BP3: 68,269,698-68,280,231 (10.5 kb): intergenic

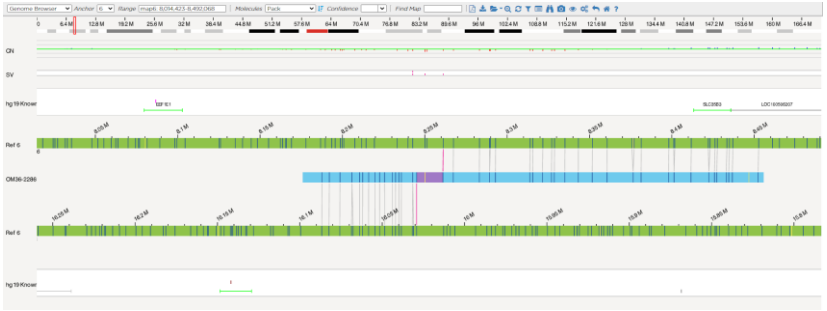
BP4: 68,922,941-68,929,233 (6,3 kb)
Disruption of the ***SYT14P1*** gene (whole gene), OMIM-Gen
no associated phenotype

Results


57 samples
54 blood samples
3 prenatal samples
37 samples with normal chromosome analysis
27 samples with normal OGM result
10 samples with abnormal OGM result
3 Samples with SV
3 x inversions
7 samples with LOH/AOH
12 AOH/LOHs

Case 6: couple w recurrent miscarriage, CA normal





inv(6)(p24.3p22.3) Größe: 7,7 Mb

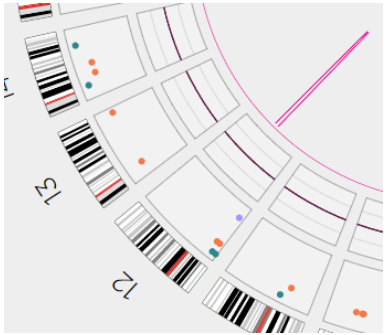
BP1 auf Chromosom 6: 8261207-8251336(9,9 kb)

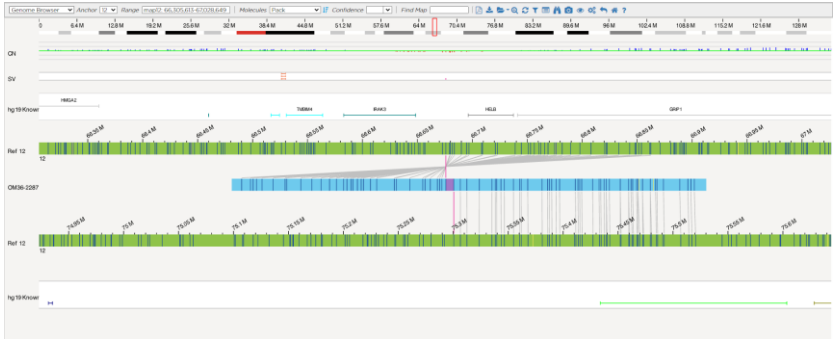
- No genes in BP

BP2 auf Chromosom 6: 16029049-16031020 (2 kb)

- No genes in BP

Confirmed by FISH





inv(12)(q14.3q21.1) Größe:8,6 Mb

BP1 auf Chromosom 12: 66675941-66672810 (3,1 kb)

- No genes in BP

BP2 auf Chromosom 12: 75300425-75291890 (8,5 kb)

- No genes in BP

Confirmed by FISH

Conclusion

- OGM allows detection of SV from 500 bp up to entire chromosomes

- comparison OGM/CA: 100% concordance
- comparison OGM/Array: 80% concordance

- Detection of different aberrations types with different sizes

→ Used as additional method but not (yet) as replacement for routinely used tests

THANK YOU

Kontakt:
Julia Flunkert
Medicover Genetics GmbH
Berlin, Germany
+49 30 92090746
Julia.Flunkert@medicover.de

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